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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,970	08/10/2001	Ashok Amin	AMIN4A	4363

7590 05/19/2004

BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, DC 20001

EXAMINER	
MOSHER, MARY	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/925,970	AMIN ET AL.
	Examiner	Art Unit
	Mary E. Mosher, Ph.D.	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1648, Examiner Mosher. ***Continued***

Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/2004 has been entered.

Claim Rejections - 35 USC § 112

Claims 35, 36, 38-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To summarize the arguments to date, claims 34 and 37 are broadly drawn to a method for treating hepatitis by administering to a patient in need thereof an effective amount of etanercept (a recombinant TNF receptor-Fc fusion protein) or infliximab.(a humanized anti-TNF monoclonal antibody). Claims 36 and 38-42 are limited to treating viral hepatitis, more specifically any of hepatitis A, B, C, D, or E. The specification provides a working example of treating one patient suffering from both rheumatoid

arthritis and chronic hepatitis C (HCV). After Etanercept treatment, reduced viral RNA and "normalized liver enzymes" were observed, in contrast to four years of abnormal liver enzymes and elevated HCV RNA prior to treatment. At or near the time of invention, at least one published report of improved indicators for HCV infection in a single infliximab-treated patient did not lead those skilled in the art to a conclusion that the method was effective for treating hepatitis. This was taken to indicate that results similar to those presented in the specification would not be convincing evidence of efficacy to those skilled in the art, and would not provide sufficient guidance to enable the treatment method claimed. A declaration filed 18 July 2003 was not found convincing.

In the response filed 2/27/2004, Dr. Abramson provides another 1.132 declaration. In seven cases, including one under his direction and six brought to his attention by other physicians, patients suffering from both rheumatoid arthritis and chronic HCV sere treated with Enbrel (Etanercept), and three responded positively to the treatment, with reduced viral load in all three and at least some improvement in liver enzymes in two. In addition, a publication by Peterson is cited as evidence that some patients respond positively to the treatment, even though Peterson did not call attention to this fact. The declaration also cites a publication by Ohta regarding HBV, and publications by Mookerjee, Tilg, and Spahr regarding alcoholic hepatitis, as providing evidence of efficacy of treatment with a TNF blocker. Dr. Abramson concludes that it is clear that some patients infected with a hepatitis virus respond positively to treatment with a TNF blocker.

However, on considering the full text of the Peterson publication, Peterson points out that there is a large expected rate of spontaneous variation in viral load, and that none of the patients, including those with a 10-fold decrease in viral load, showed clinically significant changes in liver function. It is not clear whether or not the changes in liver enzymes are clinically significant for the patients observed by Dr. Abramson; patient 1 shows fluctuation both below and above the pretreatment level, patient 2 shows no change in ALT, and patient 3 show no change in either AST or ALT. Therefore, the evidence as a whole does not indicate that etanercept or infliximab are effective for treatment of HCV, or that the guidance provided in the specification is sufficient to enable treatment of HCV hepatitis.

On considering the full text of the Ohta publication, Ohta provides evidence that anti-TNF antibody can prevent a damaging immune response directed against cells expressing HBV surface antigen when administered prior to damage, but it is not clear how this relates to treating a patient where HBV infection is not limited to expression of the surface antigen, and the liver damage has already occurred. The record is silent on efficacy against hepatitis viruses A, D, and E. Therefore, the evidence as a whole does not indicate that etanercept or infliximab is effective for treatment of viral hepatitis, absent undue experimentation.

The publications by Mookerjee, Tilg, and Spahr provide evidence that the TNF blockers are effective against alcoholic hepatitis. However, as discussed below, the prior art contains suggestions equivalent to the suggestions made in the specification for treatment of alcoholic hepatitis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Le et al, US 5,698,195. Le et al teaches anti-TNF monoclonal antibodies, similar to infliximab, and explicitly suggests use in treating alcohol-induced hepatitis, see column 35, line 42. If a suggestion to treat the condition and directions to perform routine experimentation to determine effective administration routes and dosages is sufficient to enable the invention as claimed, then the reference provides the same suggestion and guidance, rendering the invention as a whole prima facie obvious.

Claims 34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feldmann et al, WO 98/22137.Feldman teaches a treatment method comprising administering a TNF antagonist. Feldmann teaches TNF antagonists include anti-TNF antibodies, and receptor molecules which bind specifically to TNF, see the passage spanning pages 6-7; infliximab and etanercept were known species of these antagonist types. Feldmann suggests treatment of alcohol-induced hepatitis and other forms of chronic hepatitis, see page 13, lines 1-2. If a suggestion to treat the condition and directions to perform routine experimentation to determine effective administration routes and dosages is sufficient to enable the invention as claimed, then the reference

provides the same suggestion and guidance, rendering the invention as a whole prima facie obvious.

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is 571-272-0906. The examiner can normally be reached on M-T and alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

5/17/04

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800 1600